



CRISPR/Cas9-Mediated Liver Gene Knockout of *KLKB1* to Treat Hereditary Angioedema

23rd Annual Meeting of the American Society of
Gene and Cell Therapy

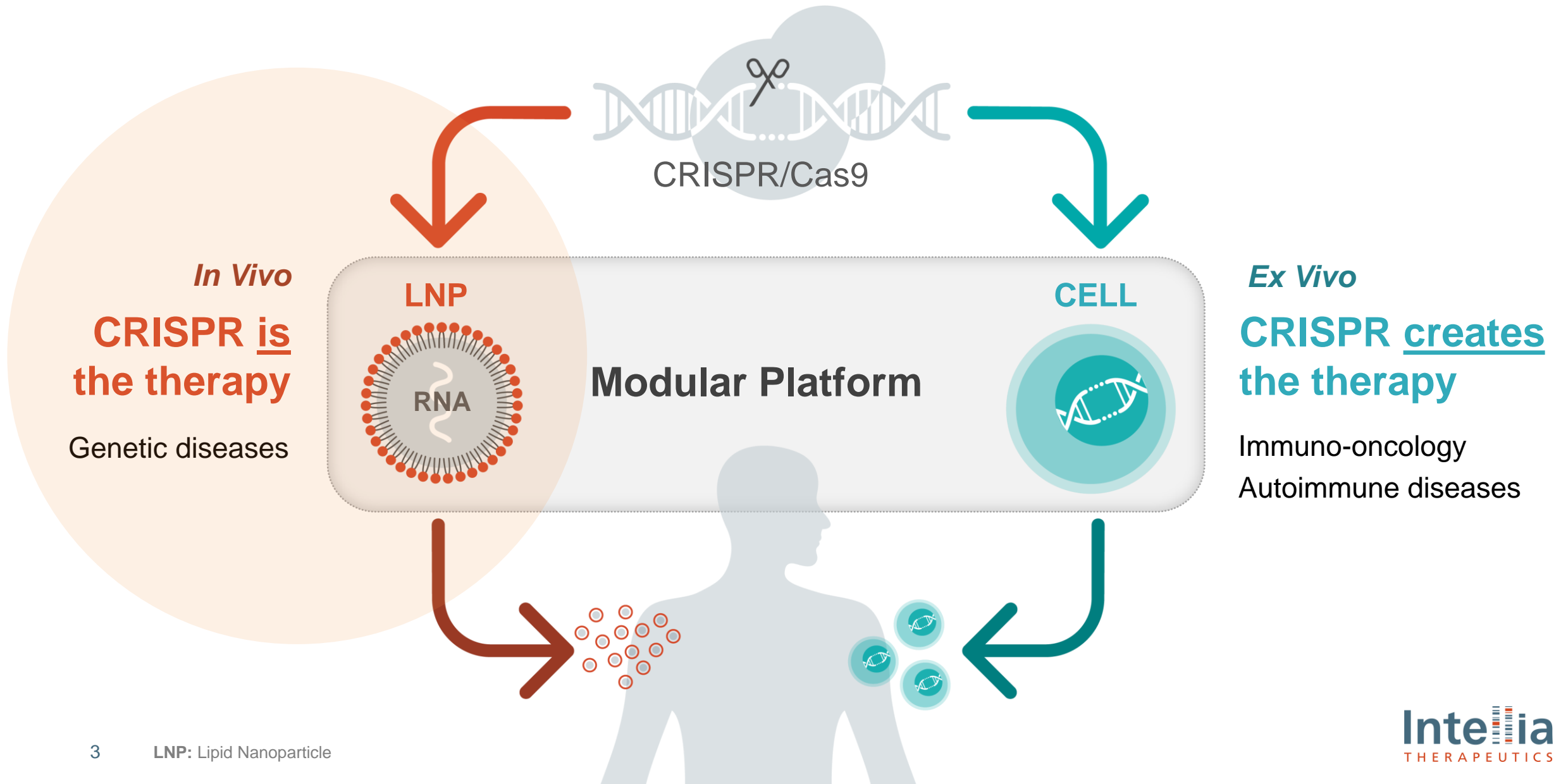
Jessica Seitzer | May 15, 2020

Intellia Therapeutics' Legal Disclaimer

This press release contains “forward-looking statements” of Intellia Therapeutics, Inc. (“Intellia” or the “Company”) within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia’s beliefs and expectations regarding its: planned submission of an investigational new drug (“IND”) application or similar clinical trial application for NTLA-2001 for the treatment of transthyretin amyloidosis (“ATTR”) in mid-2020 and its planned dosing of first patients in the second half of 2020; plans to submit an IND application for NTLA-5001, its first T cell receptor (“TCR”)-directed engineered cell therapy development candidate for its acute myeloid leukemia (“AML”) program in the first half of 2021; plans to submit an IND or similar clinical trial application for its hereditary angioedema (“HAE”) program in the second half of 2021; plans to advance and complete preclinical studies, including non-human primate studies for its ATTR program and HAE programs, and other animal studies supporting other in vivo and ex vivo programs; development of a proprietary LNP/AAV hybrid delivery system, as well as its modular platform to advance its complex genome editing capabilities, such as gene insertion; presentation of additional data at upcoming scientific conferences, and other preclinical data in 2020; advancement and expansion of its CRISPR/Cas9 technology to develop human therapeutic products, as well as its ability to maintain and expand its related intellectual property portfolio; ability to demonstrate its platform’s modularity and replicate or apply results achieved in preclinical studies, including those in its ATTR, AML, and HAE programs, in any future studies, including human clinical trials; ability to develop other in vivo or ex vivo cell therapeutics of all types, and those targeting WT1 in AML in particular, using CRISPR/Cas9 technology; ability to optimize the impact of its collaborations on its development programs, including but not limited to its collaborations with Novartis or Regeneron Pharmaceuticals, Inc., and Regeneron’s ability to enter into a co-development and co-promotion agreement for the HAE program; statements regarding the timing of regulatory filings regarding its development programs.

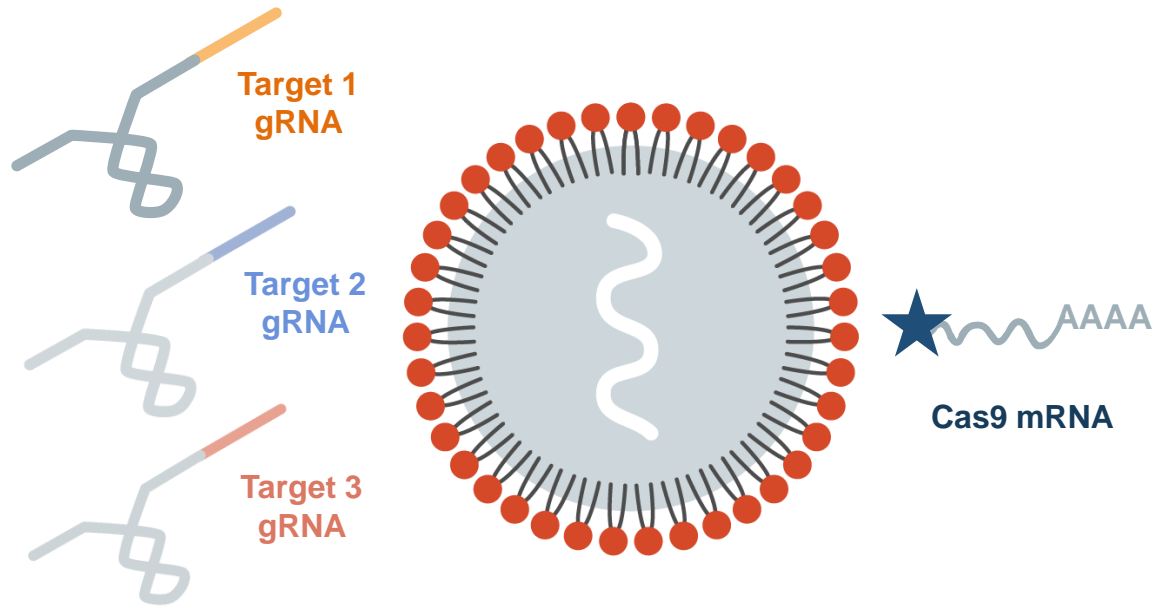
Any forward-looking statements in this press release are based on management’s current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: risks related to Intellia’s ability to protect and maintain its intellectual property position; risks related to Intellia’s relationship with third parties, including its licensors and licensees; risks related to the ability of its licensors to protect and maintain their intellectual property position; uncertainties related to the initiation and conduct of studies and other development requirements for its product candidates; the risk that any one or more of Intellia’s product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and the risk that Intellia’s collaborations with Novartis or Regeneron or its other ex vivo collaborations will not continue or will not be successful. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia’s actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in Intellia’s most recent annual report on Form 10-K as well as discussions of potential risks, uncertainties, and other important factors in Intellia’s other filings with the Securities and Exchange Commission. All information in this presentation is as of the date of the release, and Intellia undertakes no duty to update this information unless required by law.

Intellia Therapeutics is a Full-Spectrum Genome Editing Company



Intellia's *In Vivo* Liver Editing Modular Platform Employs Non-Viral Delivery

Lipid Nanoparticles (LNPs)



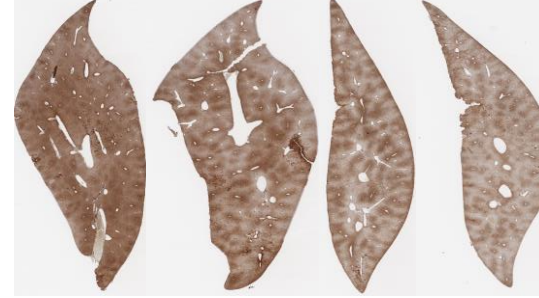
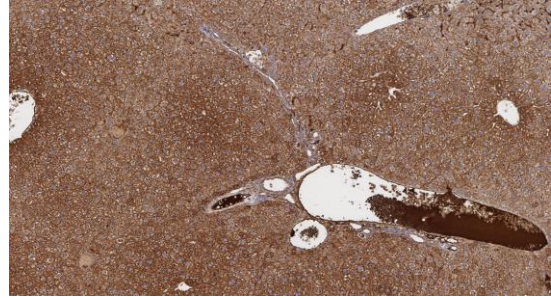
Key Advantages of LNP Delivery

- ✓ Clinically-proven delivery to liver
- ✓ Large cargo capacity
- ✓ Transient expression
- ✓ Biodegradable
- ✓ Low immunogenicity
- ✓ Well-tolerated
- ✓ Redosing capability
- ✓ Scalable synthetic manufacturing
- ✓ Tunable

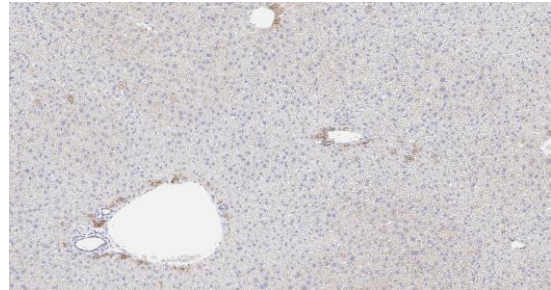
Effective Transthyretin (TTR) Liver Knockout (KO) in Mice After Single LNP Dose

Mouse TTR Immunohistochemistry (IHC)

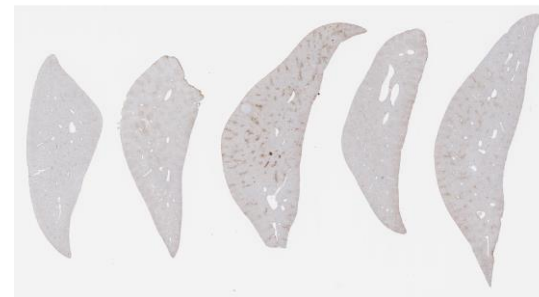
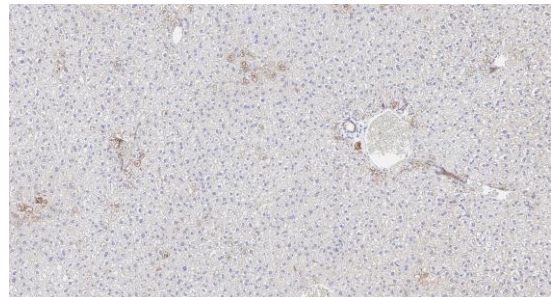
Vehicle
1 week



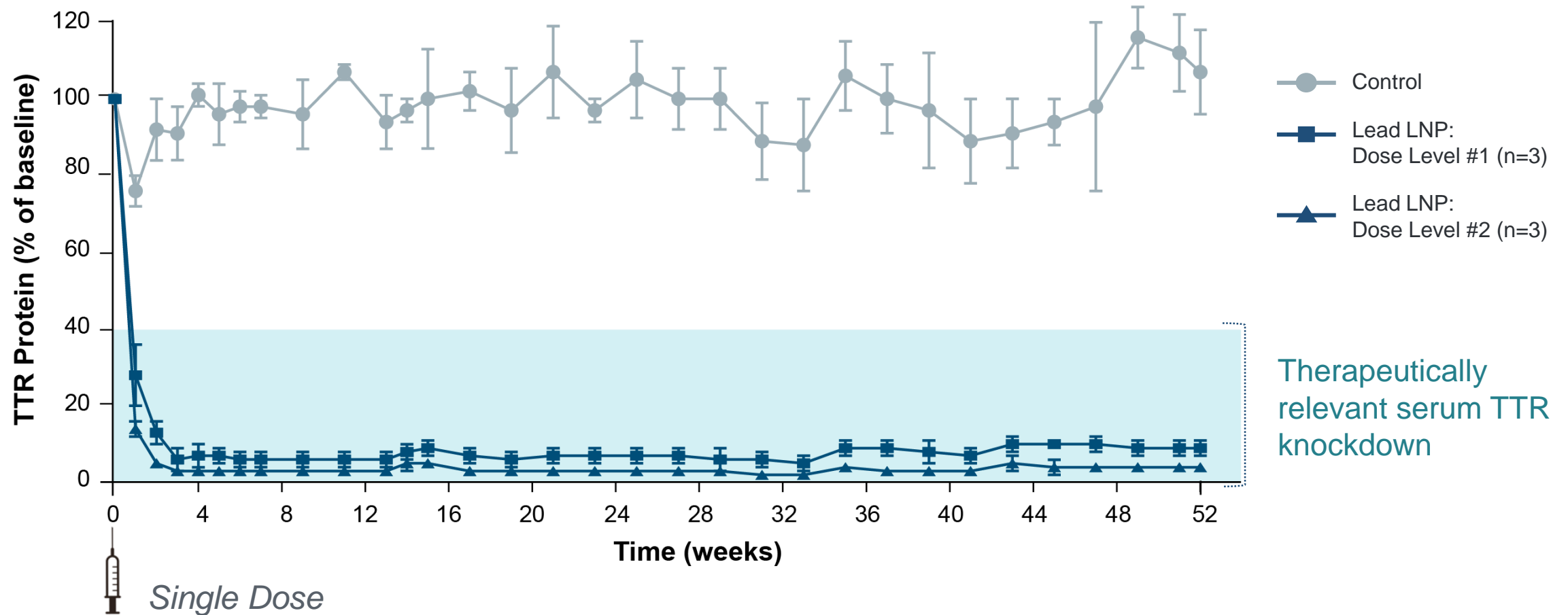
TTR Knockout
1 week



TTR Knockout
6 months



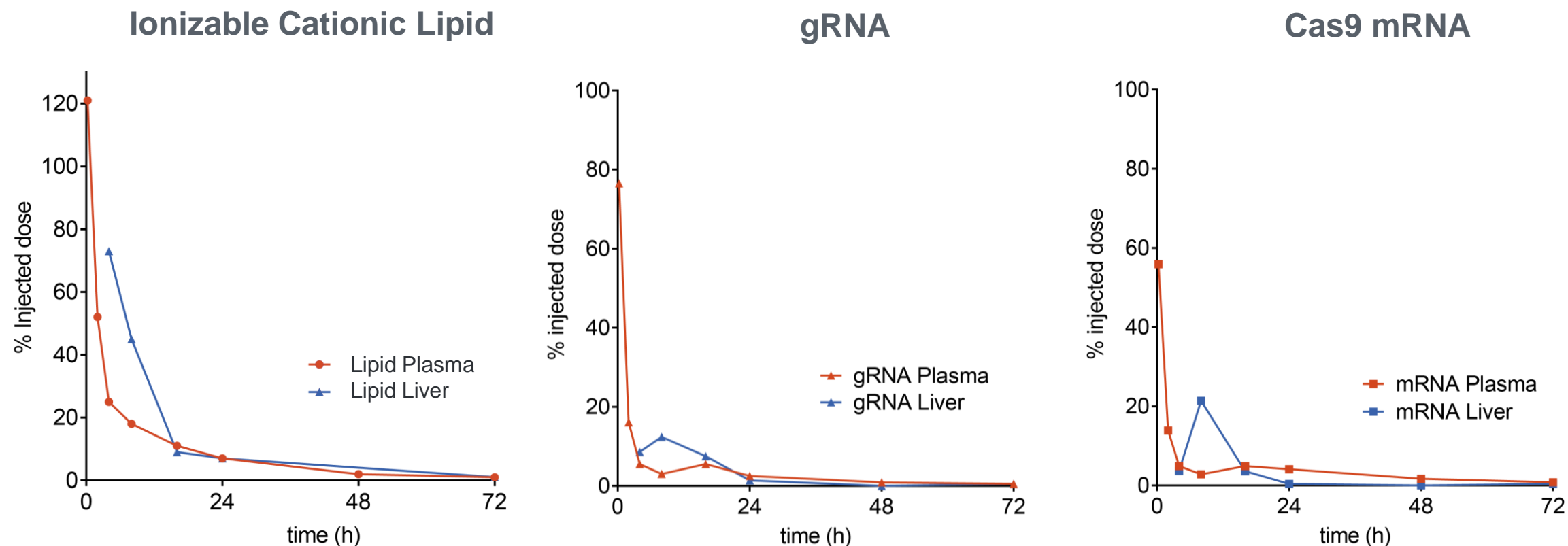
Year-Long, >95% Serum TTR KO After a Single Dose in Non-Human Primates (NHPs)



NTLA-2001 for Transthyretin (TTR) Amyloidosis

Poised to submit an IND or IND-equivalent in mid-2020

Transient Exposure to LNP and RNA Cargo After Single Administration in NHPs



Disease and Target Selection Leverage Platform Modularity



Platform Modularity



Liver LNP
Delivery



Editing
Tool



Liver Target and Disease



Unmet
Need



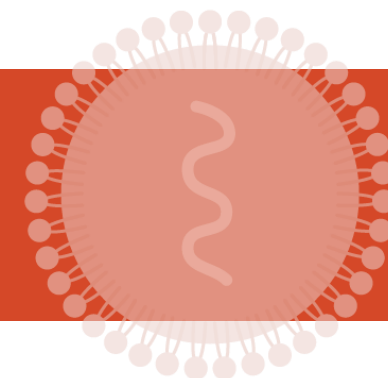
Causative
Gene



Path to the
Clinic and
Registration

Prekallikrein B1 (KLKB1) Liver Knockout for Hereditary Angioedema (HAE)

Genetic disease characterized by overproduction of bradykinin, which leads to **recurring, severe and unpredictable swelling** in various parts of the body



1 in 50,000

HAE patients¹

Airway obstruction is particularly dangerous because it can cause death by asphyxiation

Attacks can occur every

7-14 days

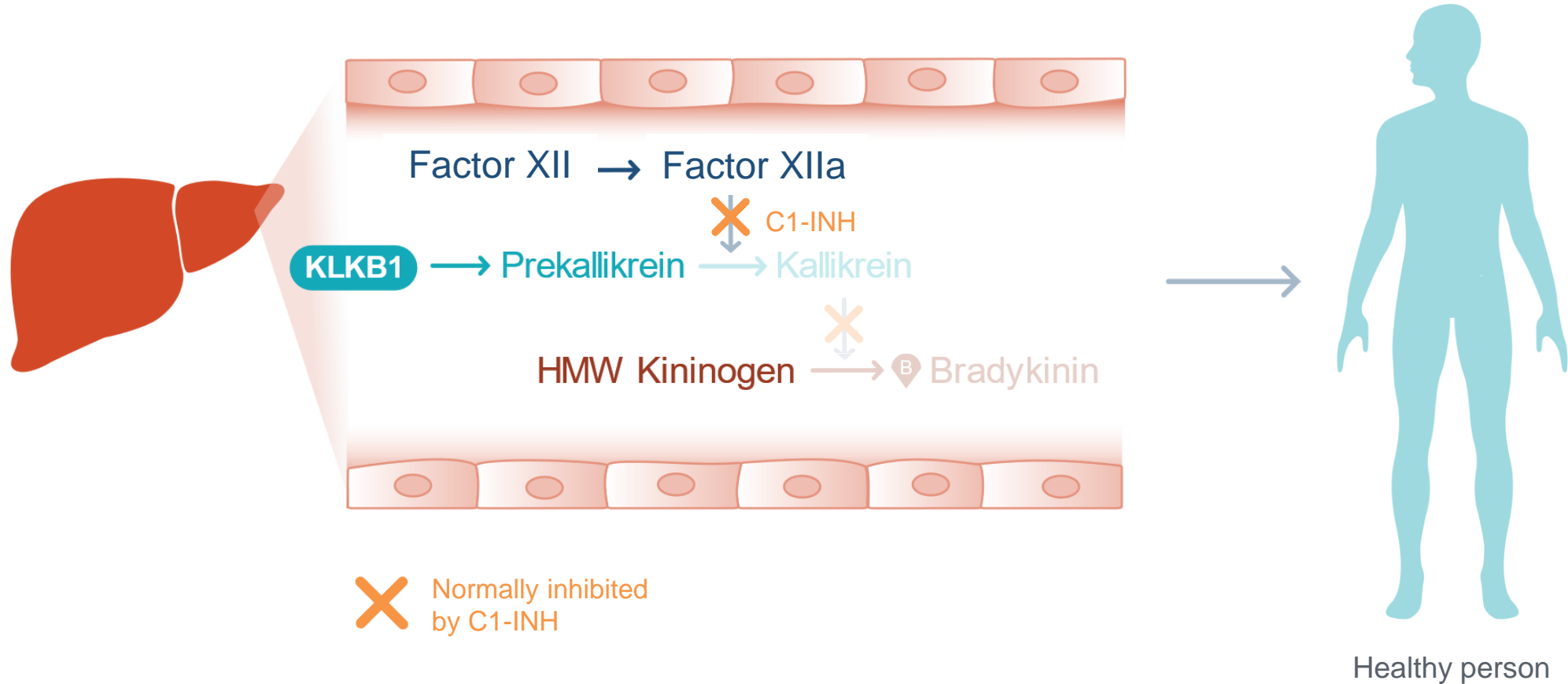
on average for untreated patients*

Only chronic treatment options currently available

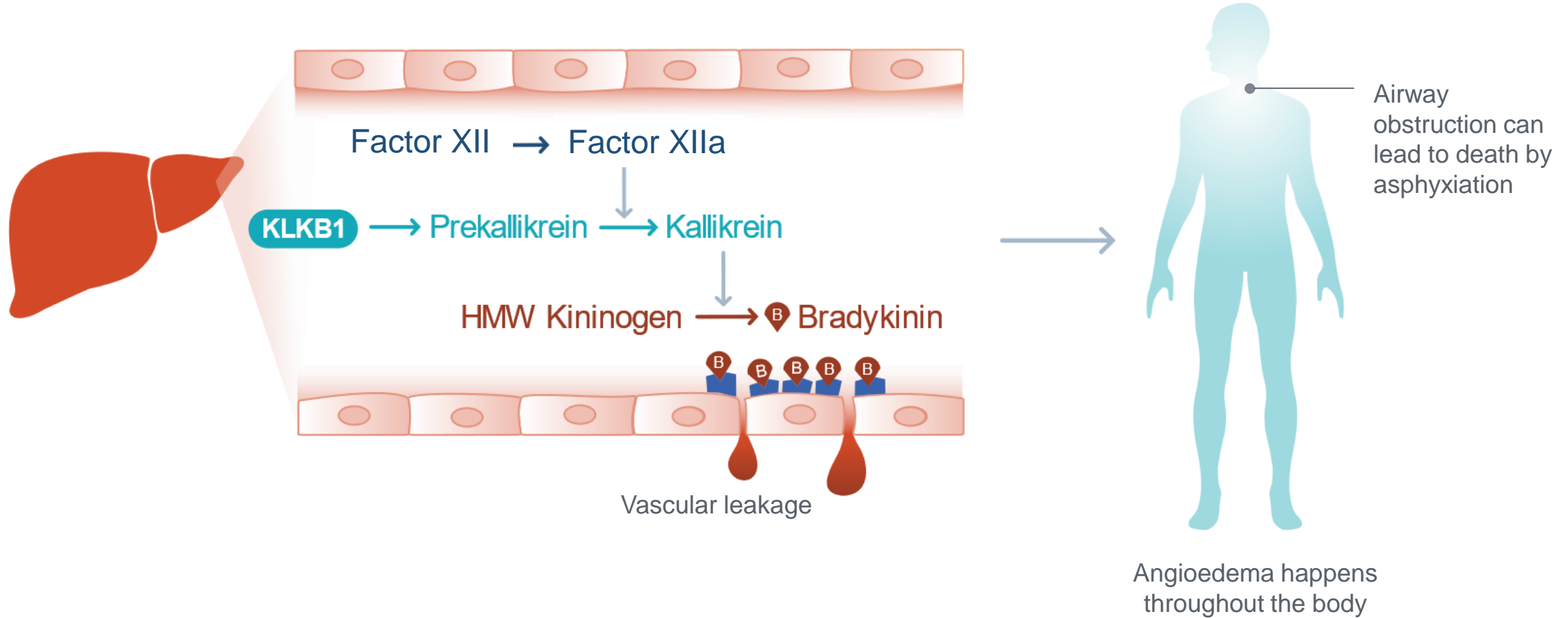
NTLA-2002 in development for HAE

- Employs a knockout edit of *KLKB1* gene in hepatocytes after single course of treatment
- Aims to reduce plasma kallikrein activity to prevent excess bradykinin production leading to HAE attacks

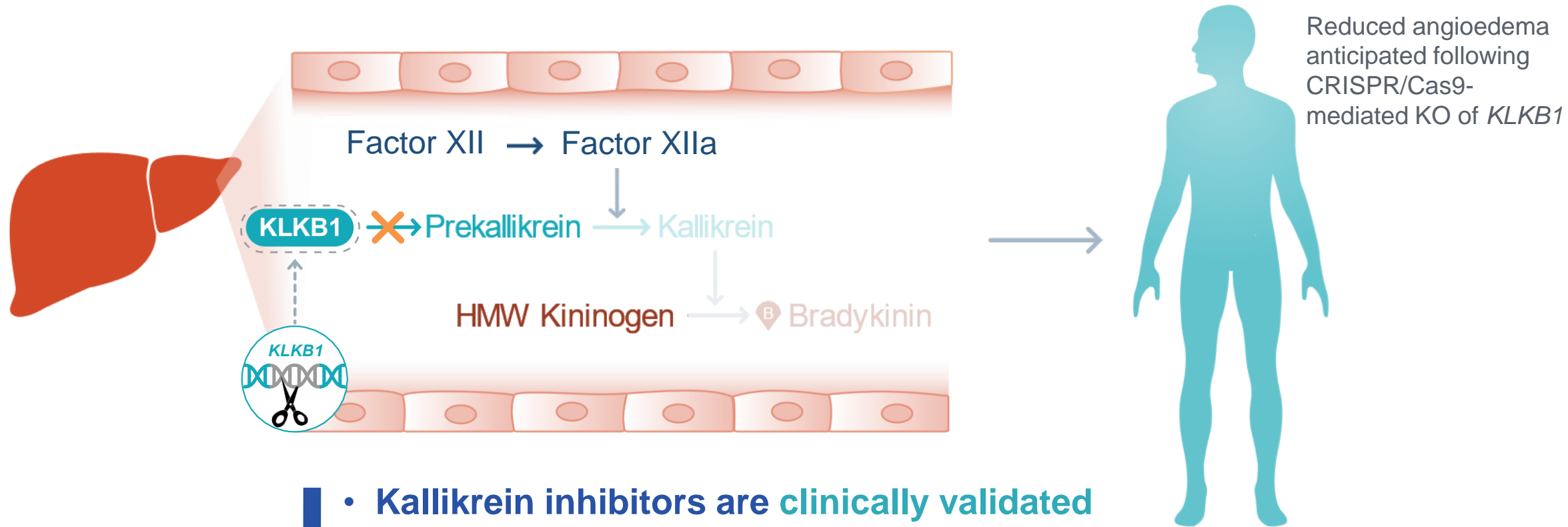
C1 Esterase Inhibitor (C1-INH) Regulates the Release and Buildup of Bradykinin



C1-INH Deficiency Results in Unregulated Release and Buildup of Bradykinin, Activating Endothelial Cells and Leading to Angioedema

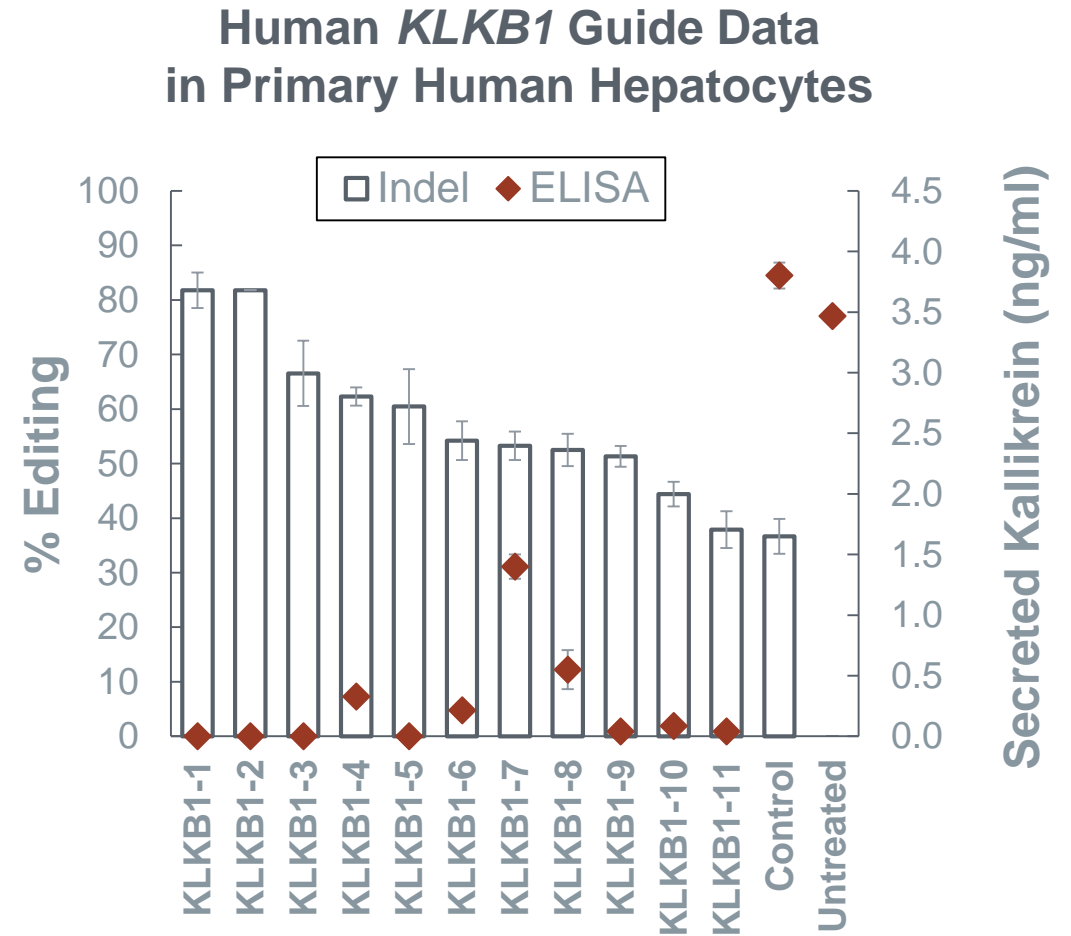
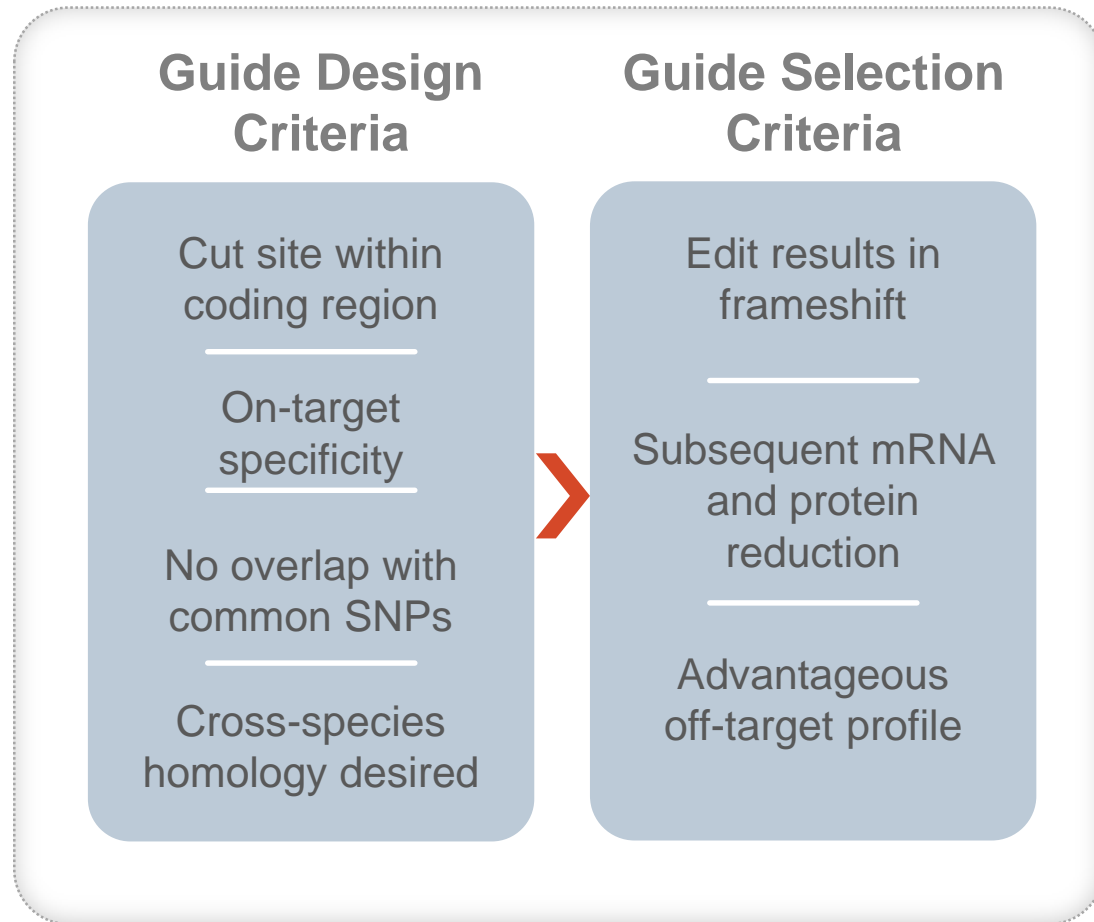


CRISPR/Cas9-Mediated KO of *KLKB1* Reduces the Undesired Bradykinin Activity in People with HAE

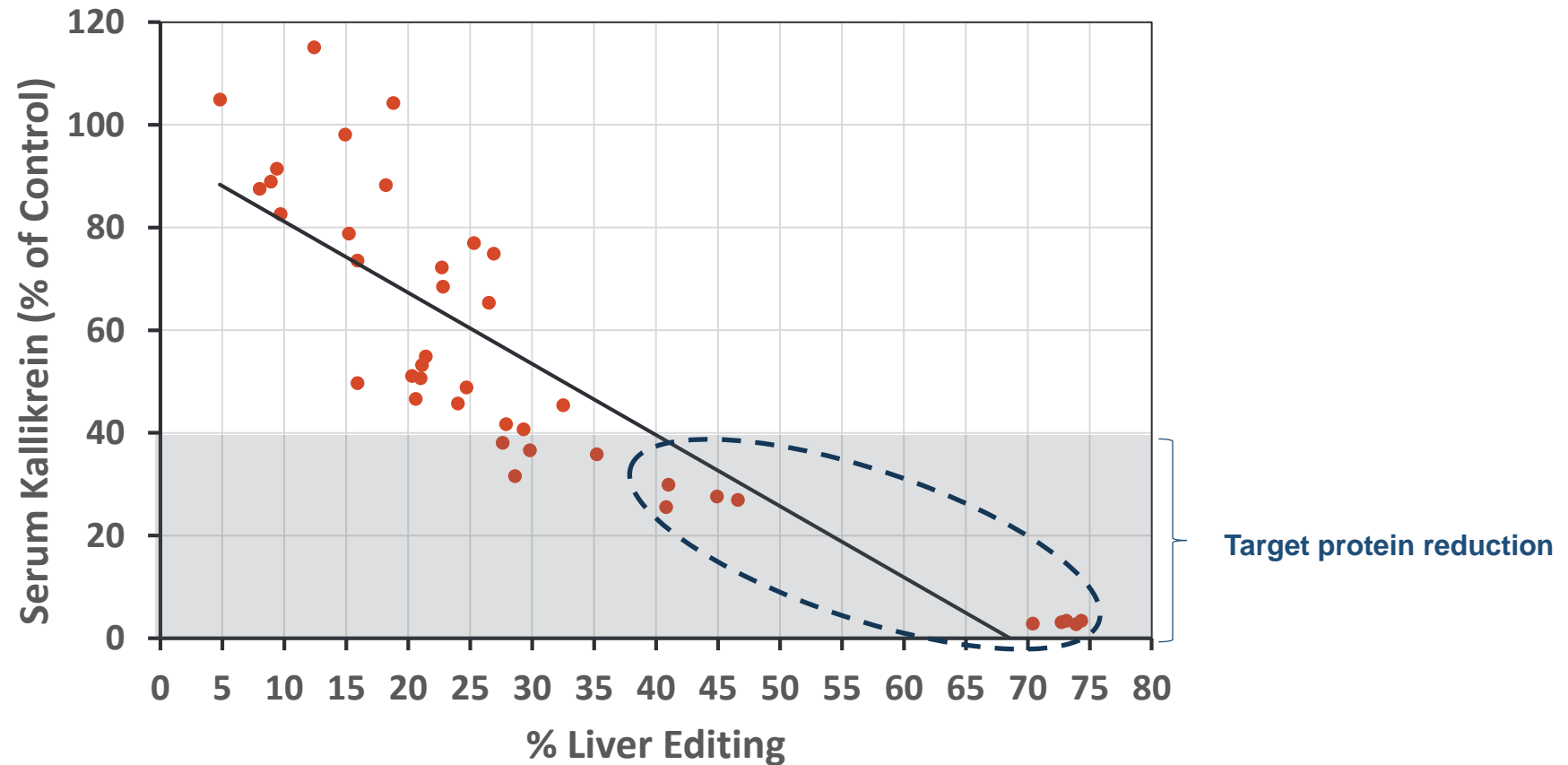
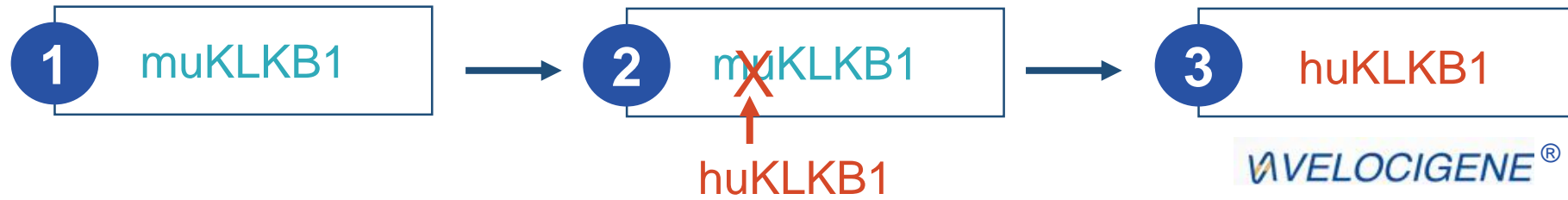


- Kallikrein inhibitors are clinically validated in preventing HAE attacks
- *KLKB1* KO is expected to be safe, as human nulls show no associated pathology*

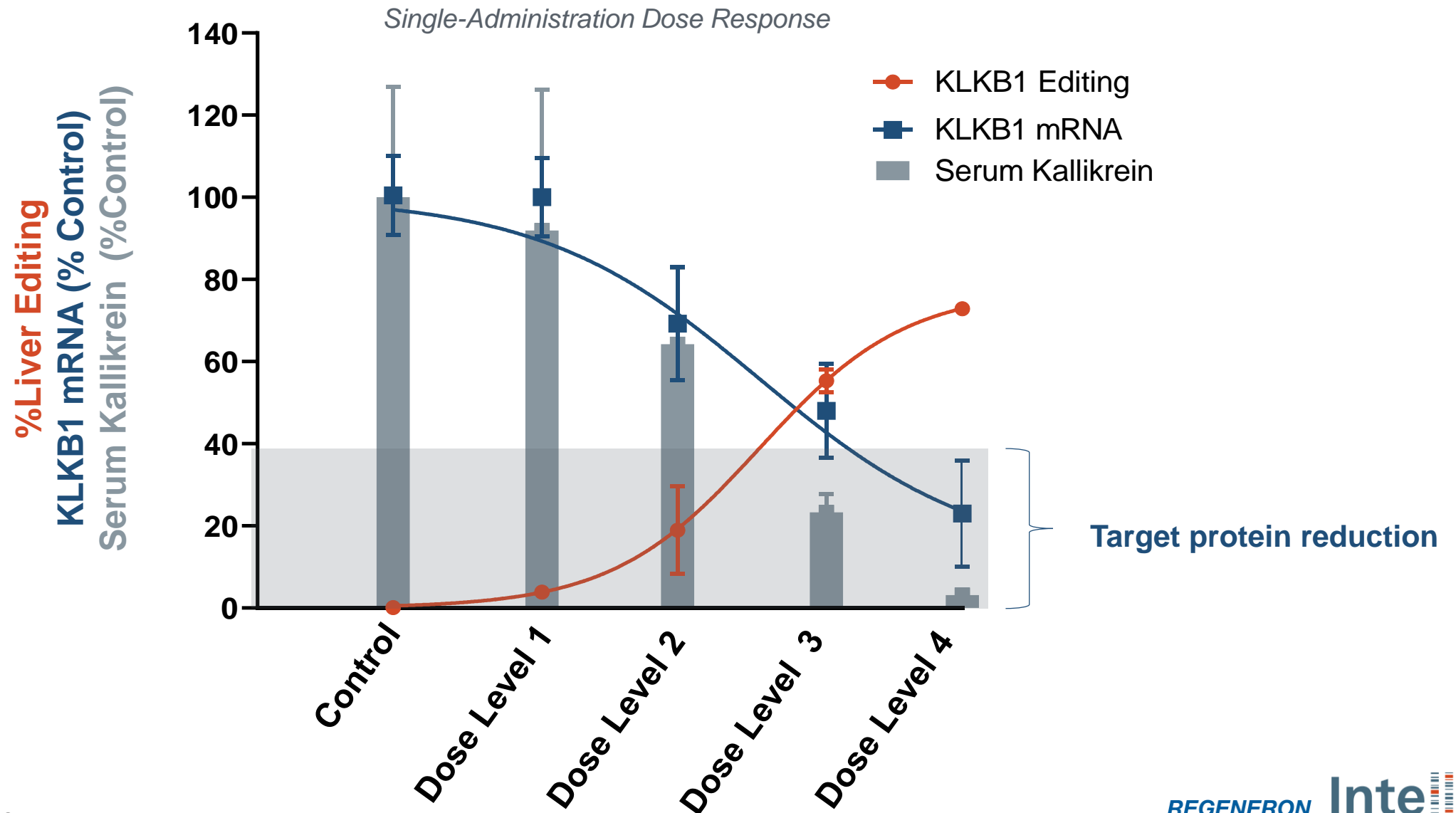
Intellia's Industrialized Guide Qualification Platform Enables Efficient Selection of *KLKB1* Human Lead Guides



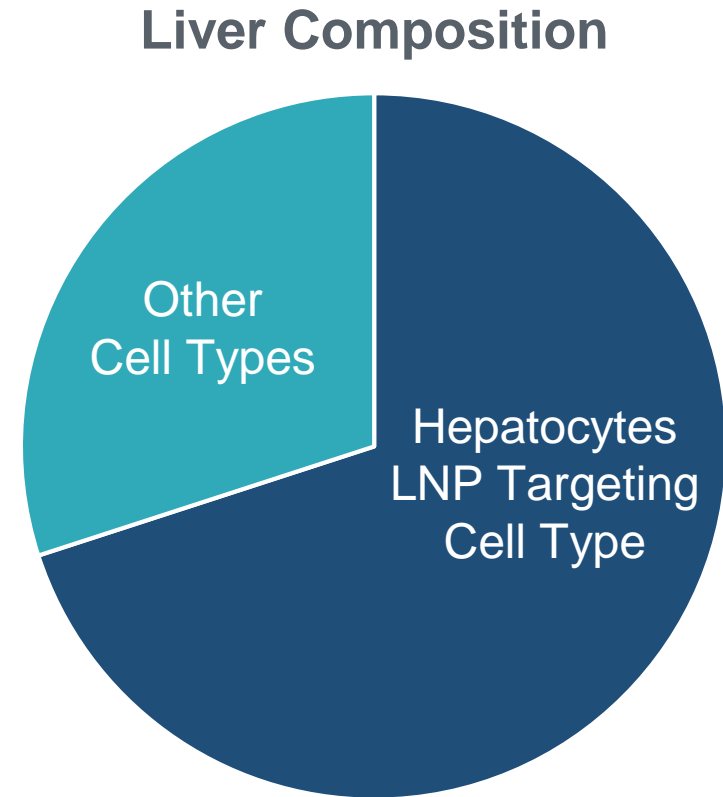
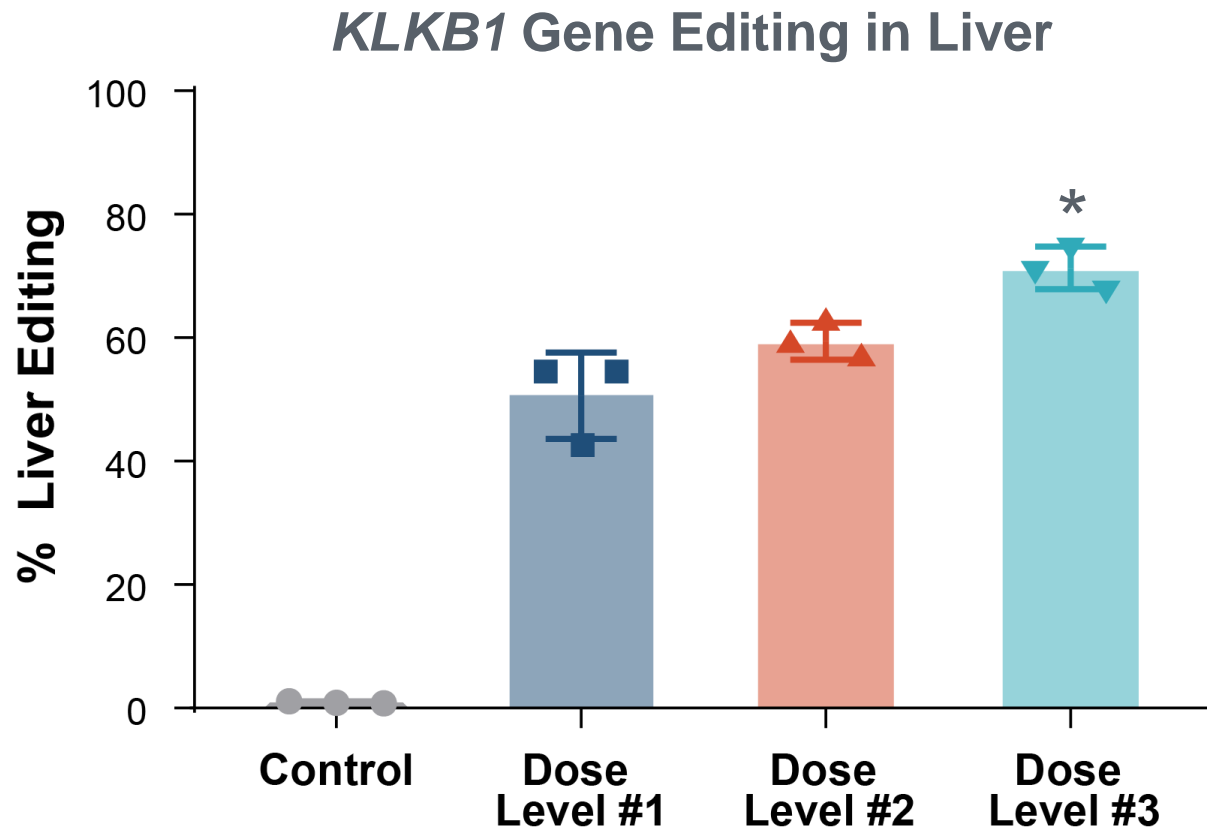
Humanized *KLKB1* Mouse Model Leveraged for Lead gRNA Selection



Dose-Dependent Editing and Subsequent *KLKB1* mRNA and Kallikrein Protein Reduction in HuKLKB1 Mouse Model with Lead Candidate gRNA

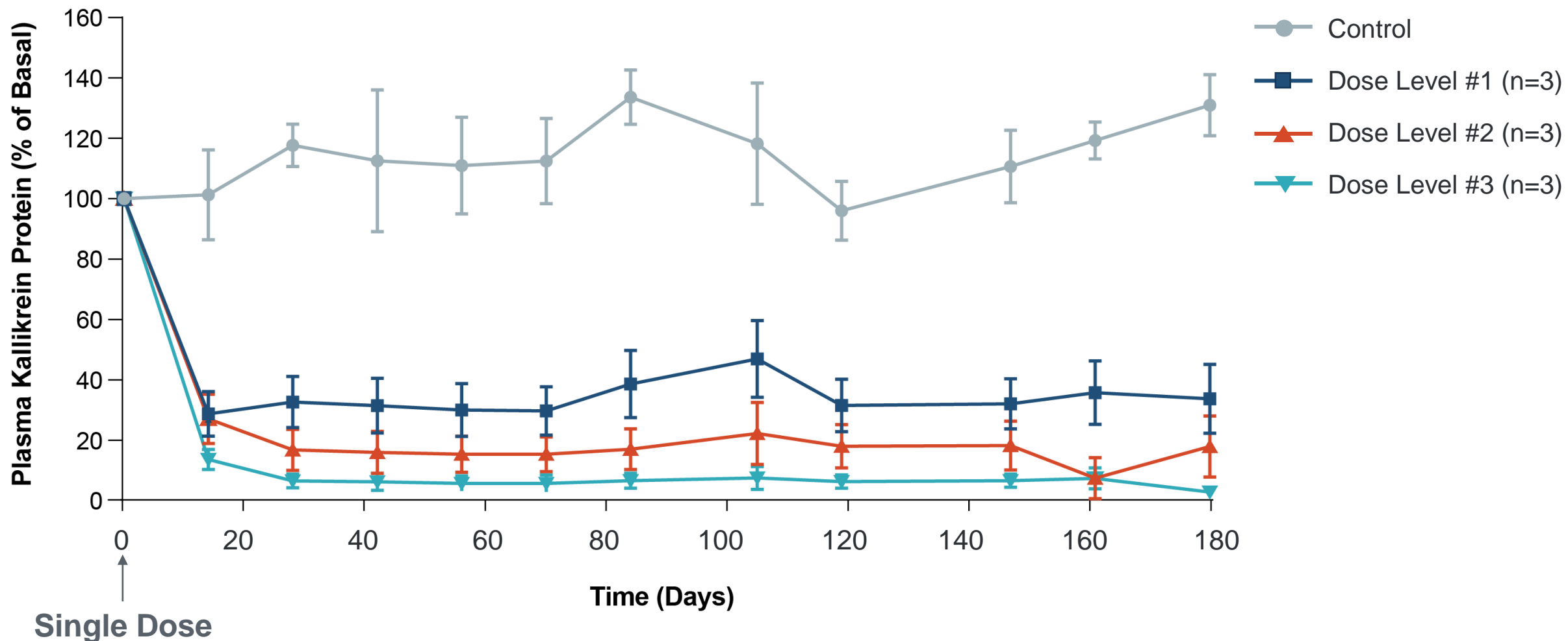


Single-Administration Dose Response in NHP Results in >70% Editing of the *KLKB1* Gene

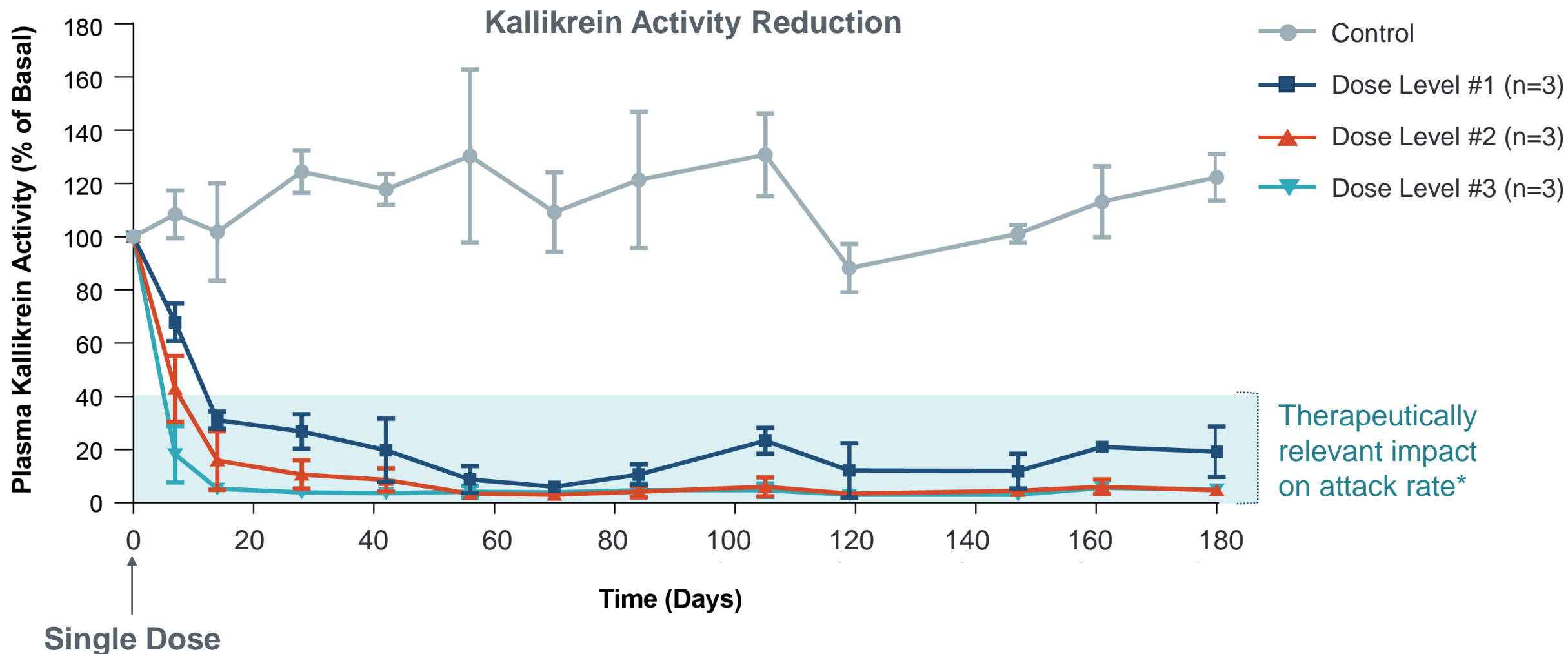


*Dose level #3 editing of >70% achieves near maximum hepatocyte editing

KLKB1 KO by Single Dose LNP in NHPs Results in Reproducible and Durable Decrease in Plasma Kallikrein Protein Levels



Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs



Key Takeaways

- HAE program builds on the foundation established for transthyretin amyloidosis (ATTR), demonstrating the **modularity of Intellia's liver gene knockout platform**
- Editing of *KLKB1* gene results in **therapeutically relevant reduction of kallikrein activity** in NHPs
- **Kallikrein activity reduction sustained for at least 22 weeks** in NHPs, in a dose-responsive manner
- **NTLA-2002 nominated as HAE development candidate** with plans to submit an IND or IND-equivalent in 2H 2021

Intellia

THERAPEUTICS